REMARKS

The present application is directed to recombinant antigens produced by baculovirus expression vectors, particularly the herpes simplex virus types 1 and 2 glycoprotein antigens designated glycoprotein G-1 (gG-1) and glycoprotein G-2 (gG-2). The baculovirus system provides high level production of the antigens in substantially pure form. The purified antigens are useful for detecting type-specific herpes simplex virus infections.

In the Office Action mailed May 28, 1997, the Examiner maintained the rejection of Claims 7, 8, and 16 under 35 U.S.C. §103 as obvious over the article by Lee, Francis K., *et al.*, "Detection of Herpes Simplex Virus Type 2-Specific Antibody with Glycoprotein G," *J. Clin. Microbiol.* 22(4):641-644 (October 1985) or the article by Lee, Francis K., *et al.*, "A Novel Glycoprotein for Detection of Herpes Simplex Virus type 1-specific Antibodies," *J. Virol. Methods* 14:111-118 (1986) in view of the article of Luckow, Verne A., *et al.*, "Trends in the Development of Baculovirus Expression Vectors," *Bio/Technology*, 6:47-55 (January 1988) or the article of Matsuura, Yoshiharu, *et al.*, "Baculovirus Expression Vectors: the Requirements for High Level Expression of Proteins, Including Glycoproteins," *J. Gen. Virol.*, 68:1233-1250 (1987). Applicants respectfully traverse.

Claims 7 and 8 are product-by-process claims wherein recombinant gG-1 and gG-2 antigens are produced by a recombinant baculovirus in which the 5' nontranslated leader sequence of the polyhedrin gene is joined to the coding region of the herpes simplex virus type 1 or 2 glycoprotein gene. Claim 16 is directed to a composition containing pure recombinant baculovirus-expressed herpes simplex virus gG-1 or gG-2 antigens in a pharmaceutically acceptable carrier.

Lee *et al.*, *J. Clin. Microbiol.* 22:641-644 (1985), teach the use of purified herpes simplex virus type 2-specific glycoprotein (gG-2) in an immunodot enzymatic assay for the detection of HSV-2 antibodies in human serum. The gG-2 antigen used by Lee *et al.* (1985) is purified from HSV-2-infected HEp-2 cells using immunoaffinity chromatography columns containing the anti-gG-2 mouse monoclonal antibodies H966 and H1206.

Lee *et al.*, *J. Virol. Methods* 14:111-118 (1986), teach the purification of herpes simplex virus type 1-specific glycoprotein (gG-1) using the mouse monoclonal antibody H1379-2.

Matsuura *et al.* teach that the polyhedrin gene promoter of *Autographa californica* nuclear polyhedrosis virus (AcNPV) is useful for high level expression of a glycoprotein of lymphocytic choriomeningitis virus. Matsuura *et al.* suggest that the synthesis is related to the integrity of the 5' non-coding region of the polyhedrin gene.

Luckow *et al.* is a review article directed to baculovirus expression vectors. Luckow *et al.* describe numerous factors affecting the expression of foreign genes by baculovirus vectors including optimizing placement of the foreign gene within the transfer vector.

Process of Producing Recombinant Antigen is Non-Obvious

Applicants respectfully submit that the claimed recombinant antigens are best described by the process by which they are produced and that this process is non-obvious over the cited references. In the Office Action mailed May 28, 1997, the Examiner stated that it would have been obvious to one skilled in the art to use the transfer vectors as taught by Matsuura *et al.* and Luckow *et al.* to produce the claimed recombinant gG-1 and gG-2 antigens.

Claims 7 and 8 specify that the recombinant gG-1 and gG-2 antigens are produced by joining the 5' nontranslated leader sequence of the polyhedrin gene to the coding region of the herpes simplex virus type 1 or 2 glycoprotein gene **precisely** at the translation initiation codon of the polyhedrin gene, without either missing any nucleotide present in the initiation codon or introducing any extraneous nucleotide at the initiation codon site. New Claim 17, which depends from composition Claim 16, also contains this language. Luckow *et al.* and Matsuura *et al.* **fail** to teach, suggest or imply joining a foreign gene to the 5' nontranslated leader sequence of a polyhedrin gene **precisely** at the 5' translation initiation codon of the polyhedrin gene. Although Luckow *et al.* mention that the placement of the foreign gene within the transfer vector is important, they fail to suggest the particular placement of the gene at the 5' translation initiation codon, which was discovered by applicants to be highly successful.

Applicants respectfully submit that one skilled in the art would not be motivated to modify the baculovirus expression vectors taught by Luckow *et al.* or the polyhedrin gene promoter taught by Matsuura *et al.* to produce the herpes simplex virus gG-1 and gG-2 antigens as claimed.

Claimed Recombinant Antigens Are Distinct

The Examiner stated that, because the claims of the present application are product-by-process claims, applicants bore the burden of providing evidence to distinguish the claimed gG-1 and gG-2 proteins over the cited references. In particular, the Examiner asked how glycosylation or methylation patterns were altered and how differences in antigenicity would allow the recombinant antigens to be recognized over the glycoproteins of the prior art.

Glycosylation Efficiencies of Recombinant Antigens

Applicants conducted experiments to compare the post-translational modifications of gG-1 and gG-2 proteins expressed in two different baculovirus systems. The gG-1 and gG-2 proteins expressed by the recombinant baculovirus pAcDSM were compared with gG-1 and gG-2 proteins expressed using the gene transfer vector pAc373. The recombinant baculovirus pAcDSM joins the herpes simplex virus type 1 or 2 glycoprotein gene precisely at the translation initiation codon of the polyhedrin gene, as claimed. In contrast, the gene transfer vector pAc373 lacks nucleotides -7 to -1 of the 5' nontranslated leader sequence of the polyhedrin gene and is therefore incapable of joining the herpes simplex virus type 1 or 2 glycoprotein gene at the translation initiation codon of the polyhedrin gene.

Applicants respectfully submit that, as described on page 25, line 20 to page 26, line 7 of the present application, the recombinant baculovirus pAcDSM produces a recombinant protein having **significantly more glycosylation** than the protein produced by the recombinant baculovirus pAc373.

Molecular Weights of Recombinant versus Non-recombinant Antigens

As explained in the Third Amendment and Response to Office Action mailed May 14, 1997 and shown in Figures 3 and 4 of the previously submitted scientific article by Sanchez-Martinez and Pellett, "Expression of HSV-1 and HSV-2 Glycoprotein G in Insect Cells by Using a Novel Baculovirus Expression Vector", *Virol.* 182:229-238 (1991), the recombinant and non-recombinant gG-1 and gG-2 proteins have **different molecular weights**. As shown in Figure 3C of the Sanchez-Martinez and Pellett article, the recombinant gG-1 appears to have a molecular weight of 42 or 43 kDa, whereas the non-recombinant gG-1 has a molecular weight between 50 and 57 kDa. As shown in Figure 4D of the Sanchez-Martinez and Pellett article, the molecular weights of recombinant gG-2 are 107, 118, 128 and 143 kDa, whereas the non-recombinant gG-2

has a molecular weight between 78 and 118 kDa. It is understood by those skilled in the art that proteins having different molecular weights patterns are structurally different.

Applicants have added new claims 18-21, which specify the particular molecular weights of the recombinant gG-1 and gG-2 antigens. Support for these new claims can be found on page 21, lines 8 and 27-28.

Cross-Reactivity of Recombinant Antigens

The claimed recombinant gG-1 and gG-2 proteins are **antigenically distinct** from the non-recombinant proteins with regard to cross-reactivity. The claimed recombinant gG-1 antigen **exhibits minimal cross-reactivity** with the claimed recombinant gG-2 antigen, whereas gG-1 antigens produced by non-recombinant methods often exhibit cross-reactivity with gG-2 antigens produced by non-recombinant means. The same results are observed with the claimed recombinant gG-2 antigen. Data demonstrating the specificity of reactions of human serum specimens with the claimed recombinant antigens is set forth in the present application in Figure 5. The results are explained on page 24 of the present specification. Basically, the data shows that a serum specimen positive for HSV-1 and negative for HSV-2, as determined by the HSV-type specific indirect hemagglutination assay (IHA), reacted with the recombinant gG-1 proteins. Similarly, a serum specimen positive for HSV-2 and negative for HSV-1, as determined by IHA, reacted with the recombinant gG-2 proteins. In addition, a serum specimen weakly positive for HSV-1 and HSV-2 by IHA reacted with the recombinant gG-1 proteins (empty triangles) and reacted weakly, but clearly, with the recombinant gG-2 proteins (full triangles).

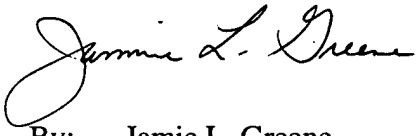
Thus, the claimed recombinant gG-1 and gG-2 antigens are both structurally and functionally distinct from gG-1 and gG-2 antigens produced by other known methods.

Conclusion

In conclusion, applicants respectfully submit that Claims 7, 8 and 16-21 are non-obvious in view of the references cited by the Examiner.

Applicants maintain that the claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited. If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 818-3773 is courteously solicited.

Respectfully submitted,
JONES & ASKEW



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